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TITLE: A Pharmacokinetic/Pharmacodynamic Study of the Glucocorticoid Receptor Antagonist Mifepristone Combined with Enzalutamide in Castrate-Resistant Prostate Cancer

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14. ABSTRACT

This is a Clinical Exploration Award funding a clinical trial for patients with metastatic, castration resistant prostate cancer (CRPC). For patients with metastatic CRPC, there are few established therapeutic options and the prognosis remains dire. The overarching goal of this award is to build on concept that under the selective pressure of androgen receptor (AR) targeted therapies, prostate cancer adapts. One way it adapts is by upregulating another hormone receptor, the glucocorticoid receptor (GR), which may compensate for diminished AR activity. The clinical trial within this award is a phase I/II clinical trial of the GR antagonist mifepristone in combination with the FDA-approved AR antagonist enzalutamide. The first objective is, within the context of a phase I clinical trial, to establish safe and pharmacologically active doses of the two drugs for use in combination for daily dosing. The second objective is to use pharmacodynamic biomarkers to support the hypothesis that GR antagonism in combination with AR antagonism will delay CRPC progression. During the second year of this award, the trial accrued to the phase I portion. The phase I study has completed the third dosing cohort. Thus far the combination of mifepristone and enzalutamide has been well tolerated with no dose limiting toxicities. Based on safety and pharmacokinetics it is anticipated this will be the recommended phase II dose, and that the phase II will start Q2 2016. Site selection for phase II underway.

15. SUBJECT TERMS
Castration resistant prostate cancer (CRPC); Androgen Receptor (AR); Glucocorticoid receptor (GR); Enzalutamide; Mifepristone; Pharmacokinetic (PK) Pharmacodynamic (PD); Prostate specific antigen (PSA)

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1 INTRODUCTION:

This award is a Clinical Exploration Award funding a clinical trial for patients with metastatic, castration resistant prostate cancer (CRPC). For patients with metastatic CRPC, there are few established therapeutic options and the prognosis remains dire. The overarching goal of this translational research award is to build on concept that under the selective pressure of androgen receptor (AR) targeted therapies, prostate cancer adapts. One way it adapts is by upregulating another hormone receptor, the glucocorticoid receptor GR), which may compensate for diminished AR activity. The clinical trial within this award is a phase I/II clinical trial of the GR antagonist mifepristone in combination with the FDA-approved AR antagonist enzalutamide. The two major objectives of the award correspond to the two phases of the trial that will be articulated in more detail within the "Accomplishments" section of the report. The first objective is within the context of a phase I clinical trial to establish safe and pharmacologically active doses of the two drugs for use in combination for daily dosing. This will be completed at the lead site. The second objective is to use pharmacodynamic biomarkers to support the hypothesis that GR antagonism in combination with AR antagonism will delay CRPC progression. This portion of the study will be a multiple-institutions study, lead by the lead site.

2 KEYWORDS

The following are key words that will be used in this report
Castration resistant prostate cancer (CRPC)
Androgen Receptor (AR)
Glucocorticoid receptor (GR)
Enzalutamide
Mifepristone
Pharmacokinetic (PK)
Pharmacodynamic (PD)
Prostate specific antigen (PSA)

3 ACCOMPLISHMENTS:

A. What were the major goals of the project?

Please note that a revised statement of work (SOW) was submitted and approved 11/2015 as was a no-cost extension allowing for 48 month study duration.

As stated in the revised SOW, the major tasks for the study, with projected timeline are listed as follows. Specific activities accomplished, in concordance with SOW during this quarter will be detailed in the next section.

Major Task 1: Regulatory Approval: Lead and subsidiary sites	**Months 1-30**
Major Task 2: Coordinate and Initiate Phase I Portion of Study	**Months 1-9**
Major Task 3: Complete phase I study	**Months 1-27**
Major Task 4: Initiation of Phase II	**Months 25-30**
Major Task 5: Complete Phase II study	**Months 27-48**
Major Task 6: Data Analysis	**Months 27-48**

B. What was accomplished under these goals?

The following tables summarize the objectives/subtasks to be accomplished during this reporting period specifically, with comments when pertinent.

Major Task 1: Regulatory Approval: Lead and subsidiary sites			
	Timeline (months)	**Objective complete**	**Findings, developments, discussion points**
Subtask 1: Obtain Regulatory Approval for Research Protocol at UC: COMPLETE			
Subtask 2: Obtain Regulatory Approval for Research Protocol at PCCTC sites			
PCCTC site identification	1-3	Partial	Trial summary sent to PCCTC sites, several sites interested. One site (Duke Cancer Center) has agreed to participate and two others (Michigan, Johns Hopkins) are considering internally. Two other sites outside of the PCCTC (Northwestern University, Illinois Cancer Care) are interested and will be included in the study should the other two PCCTC sites decline. Will continue to give progress report to PCCTC sites and have a scheduled conference call 03/2016, at which time it is anticipated the phase II will be starting.
Scientific and IRB submission at PCCTC sites	25-28	No	Sites wish to wait until phase I complete or near complete to submit regulatory documents.
Coordination of Clinical Trials Agreement (CTA) at PCCTC sites	25-28	Partial	Sites wish to wait until phase I complete or near complete. However, active central CTA agreements are already in place between the University of Chicago and PCCTC sites as well as University of Chicago and Northwestern and Illinois Cancer Care.
Scientific Review Approval PCCTC sites	25-28	No	Sites wish to wait until phase I complete or near complete.
IRB Approval PCCTC Sites	25-30	No	Sites not committed at this point. Discussions ongoing. Sites wish to wait until phase I complete or near complete.

Major Task 2: Coordinate and Initiate Phase I Portion of Study			
	Timeline (months)	**Objective complete**	**Findings, developments, discussion points**
Finalization of data capture forms	1-3	Yes	
Site initiation training at UC	1-3	Yes	
Screening and Registration of first patient on phase I at UC	1-3	Yes	

Major Task 3: Complete phase I study	Timeline (months)	Objective complete	Findings, developments, discussion points
Recruitment and enrolment	1-24	Partial	Final cohort is accrued. Awaiting PK analysis to be done 02/2016 to confirm appropriate dose for phase II.
PK analysis	3-27	Partial	First two PK analyses complete
Weekly institutional data safety monitoring board	1-36	Yes	Ongoing
Monthly safety/oversight teleconference	27-48	NA	Will begin with multi-site participation
Submission of year 1 IND report to FDA	9-12	Yes	Year 2 IND report also submitted
Submission of any protocol amendments to IRB, FDA, HRPO	Continuous	Yes	Personnel and minor clarification amendments submitted to IRB. No significant changes that mandated HRPO submission
Milestone Achieved: Completion of phase I study	9-12	Partial	

***Note: No items within SOW to be completed on tasks 4-6 during this reporting period**

Discussion of Accomplishments:

Within this reporting period (year 2) the primary task has been to complete the phase I portion of the study. Due to the 60 day DLT periods and more dosing cohorts needed then initially anticipated, as well as commercial enzalutamide supply hurdles, this has taken longer then anticipated. However, based on PK analyses from the first 2 cohorts, it is extremely probable that the current cohort that has just completed accrual will be the final dose escalation cohort. Thus, the phase II portion will be able to proceed as outlined in the revised SOW. Subtask 2 involved opening the trial at other sites, with multiple sub-objectives outlining this task. This task is not yet complete; however progress has been made. The major barrier to this task completion is that other academic sites are not willing to commit to opening the phase II portion of the trial until the phase I portion of the trial is near complete (in the expansion cohort). Duke Cancer Center has agreed to participate and Johns Hopkins and Michigan are internally considering. We have two back-up sites identified through "The University of Chicago Personalized Cancer Care Consortium (PCCC)", which is led by senior co-investigator on this trial, Dr. Walter Stadler. Central clinical trial agreements are in existence between the University of Chicago and PCCTC sites as well as the University of Chicago and PCCC sites, which will expedite opening the trial when the phase I is complete (Task 3).

Task 2 is complete with no details to report. Data capture of enrolled patients at the University of Chicago is ongoing without issue. Task 3 is centers around completion of the Phase I clinical trial as described above. Several of the objectives within this task are complete as described within the table and as noted above.

Table 1. Patient Demographics

	40mg	*80mg*	*120mg*
N	6	6	6
Ave age	73	72.	68.

Baseline PSA (median)	13.1	54.3	171.3
Baseline PSA (range)	1.53-34.3	4.74-101.8	2.89-255.6
Caucasian (%)	66	50	83
African American (%)	33	50	17

The phase I trial is primarily safety and PK based. This reporting period has seen accrual completion of the second (80mg enzalutamide/300mg mifepristone daily) and third (120mg enzalutamide/300mg mifepristone daily) dosing cohorts. The demographics and baseline PSA are described within Table 1. The age and ethnic background is well balanced and consistent with our prostate cancer population as a whole. Of note, cohort three had a substantially higher baseline starting PSA as a cohort. Enzalutamide is the FDA approved backbone of this trial. Due to safety and PK concerns, the dose of enzalutamide and mifepristone for the initial cohort were conservatively set at 40mg enzalutamide and 300mg mifepristone. The results of this cohort were reported in last year's report. The second cohort was 80mg enzalutamide and 300mg mifepristone. The PK ratio for this cohort was 0.70 (70%), with 0.75-1.5 being acceptable for phase II expansion assuming suitable safety. The third cohort, which is 120mg enzalutamide and 300mg mifepristone, is therefore likely to be recommended phase II dose. This cohort has completed accrual, with PK analysis scheduled for 02/2015. The two drugs in combination have been well tolerated, with the most common side effect being fatigue (1 grade 3, not in DLT period, 4 other patients with grade 2). Fatigue is multifactorial, and likely due to disease, as well as the two study drugs enzalutamide and mifepristone. from There have been no dose limiting toxicities identified to date. Table 2 summarizes the most common adverse events, irrespective of cause (grade 2 or higher).

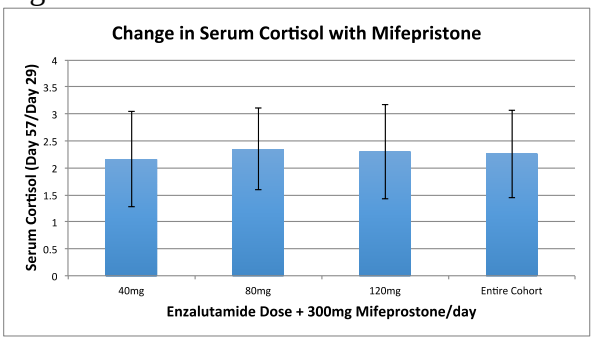
Table 2. Cumulative Adverse events to date (through n=14)

Adverse Event	*Grade 1 (n,%)*	*Grade 2 (n,%)*	*Grade 3 (n,%)*
Agitation		1, 7.1	
Amnesia	2, 14.3	1, 7.1	
Arthralgia		1, 7.1	
Back Pain	1, 7.1	1, 7.1	
Confusion	1, 7.1	1, 7.1	
Depression		1, 7.1	
Fatigue	6, 42.9	5, 35.7	1, 7.1
Gynecomastia		1, 7.1	
Hot Flashes	2, 14.3	2, 14.3	
Hypoglycemia		1, 7.1	
Insomnia		1, 7.1	
Myalgia		1, 7.1	
Nausea	3, 21.4	2, 14.3	
Pain	7, 50	2,14.3	
Pneumonitis		1, 7.1	
Rash		1, 7.1	
Urinary Incontinence	3, 21.4	1, 7.1	

From a PD standpoint, serum cortisol levels were measured before and after mifepristone at 300mg. Cortisol routinely doubled as expected, indicated on target GR antagonism. The per cohort change in cortisol is displayed graphically in Figure 1. It is therefore anticipated that

300mg mifepristone is sufficient GR antagonism and that this will be the phase II dose of mifepristone.

Figure 1



With respect to efficacy, enzalutamide+mifepristone has lowered PSA as anticipated (Figure 2).

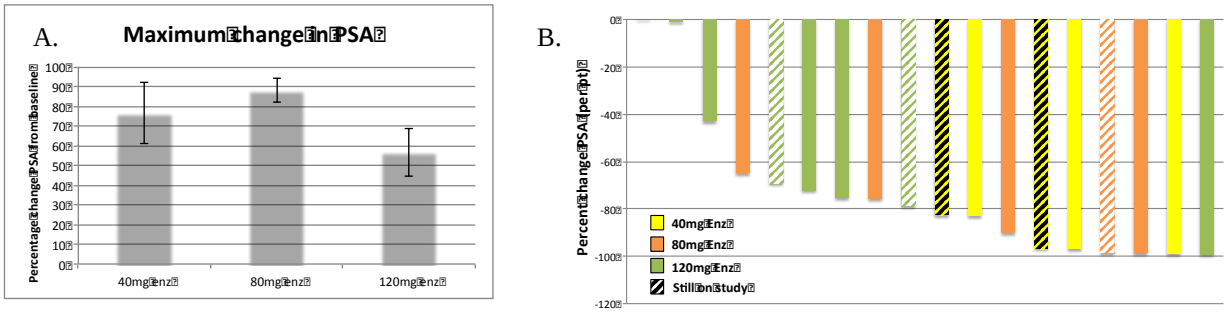
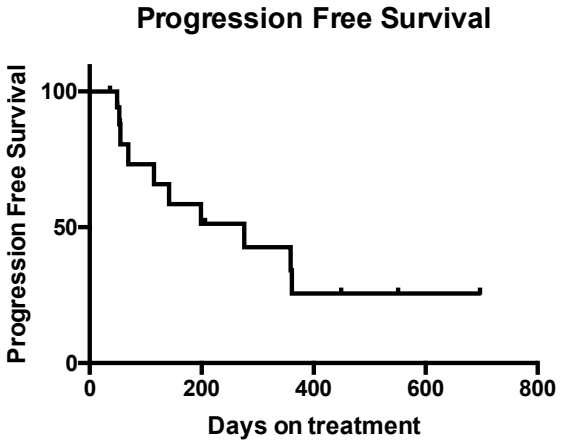


Figure 2. PSA Change During Phase I Portion of the Study. A. Per dosing cohort average change in PSA +/- standard deviation. B. PSA waterfall plot showing maximal change in PSA. Bars with diagonal lines represent patients who are still on study.

Progression free survival (PFS) for the entire cohort to date is shown in Figure 2. Median PFS is 276 day (9.8 28 day cycles), which is in line with reported PFS in phase III study of enzalutamide (8.3 months, Scher et al, *New England Journal of Medicine*, 2012).

Figure 2. Progression Free Survival for Phase I Population



Assuming PK analysis shows appropriate enzalutamide levels as expected, the cohort will be expanded to 8-12 patients (from 6) per protocol to complete the phase I study. Other sites will be engaged to route to scientific review board and IRB's as in the table at the during this cohort expansion as the recommended phase II dose will be established at this point.

Also of note, the PI has re-submitted the study to Astellas/Medivation, manufacturer of enzalutamide. Based on the current dosing levels, they have now agreed to supply enzalutamide free of charge to patients participating in the phase II of this study. This will tremendously aid in accrual, as insurance approval of enzalutamide has been an unanticipated barrier to date.

C. What opportunities for training and professional development has the project provided?

This award was not intended for professional development as it is not a training award. Nonetheless, the trial has allowed the PI, a junior investigator, to work as a lead investigator on a complex, multi-site clinical trial. As such provided the PI an opportunity to present trial progress at the PCCTC semi-annual meeting in October 2015. This meeting was attended by representatives from ~15 leading prostate cancer research institutions and included multiple thought leaders in the field. The PI was able to share trial progress and garner support in the group for the trial, which was an excellent learning opportunity.

D. How were the results disseminated to communities of interest?

There were no results to report during this reporting period.

E. What do you plan to do during the next reporting period to accomplish the goals?

The principal goal during the next reporting period is to complete Task 3 (phase I clinical trial) and initiate Major Task 4 (initiation of the phase II portion of the trial). The discussion of Task 3 was detailed above in section 3.B. During the dose expansion of the phase I at the recommended phase II dose, sites will be finalized for participation and regulatory documents will be disseminated so that full accrual to the phase II can begin without any hindrances.

4. IMPACT:

A. What was the impact on the development of the principal discipline(s) of the project?

The clinical trial has not completed and we do not have full results. Therefore, there are no significant impacts to the prostate cancer field as of yet. However, one key impact is that our trial is the first to our knowledge of enzalutamide in combination with another drug that is a pharmacologic inhibitor of enzalutamide metabolism. Enzalutamide metabolism is complex and involved multiple hepatic enzymes. We have shown that a strong inhibitor of CYP2C8/9 and CY3A4 essentially decreases clearance of enzalutamide by half. Beyond our trial, these data may have an impact as enzalutamide is considered in combination with other drugs.

B. What was the impact on other disciplines?

This study is the first study of mifepristone at 300mg daily dosing in an advanced cancer population. GR antagonism is a potential therapeutic maneuver for other cancers, such as breast cancer. We have shown that daily dosing of mifepristone

in patients with advanced cancer is safe. This is impactful as the knowledge of its safety in this population can be used as the drug is developed in other cancers.

C. What was the impact on technology transfer?
Nothing to report

D. What was the impact on society beyond science and technology?
Nothing to report

5. CHANGES/PROBLEMS:

A. Changes in approach and reasons for change
There have been no changes in approach to this research award.

B. Actual or anticipated problems or delays and actions or plans to resolve them
It should be noted that there were barriers to fully accomplishing Major Task 3 during this reporting period. Accrual to the trial was slower then anticipated. We initially had a verbal agreement with Medivation who were to supply enzalutamide for this trial (Mifepristone is being supplied by Corcept Therapeutics). Rights to enzalutamide in the United States were sold to Astellas, and Astellas refused to provide enzalutamide for the trial. Although the FDA label for enzalutamide includes such dose reduction for use in combination with other medications that may inhibit enzalutamide metabolism, Astellas was not willing to assist our trial. As an alternative to enzalutamide being provided by Medivation/Astellas, patients are still enrolling on the trial, but get enzalutamide through their commercial pharmacy. This has slowed accrual as prior authorizations are required and there is often a very high cost to the drug, even with insurance, that has somewhat limited the patient population eligible for the drug. Accrual was also held for ~4 weeks twice for PK analyses per protocol. The phase I portion of this study is necessarily slow as the dose limiting toxicity period for each cohort is 60 days on trial. Nonetheless we have recently completed accrual to the third cohort, which as stated, will likely define the recommended phase II dose. Also, as noted, the PI has re-submitted the study to Medivation/Astellas, who have now agreed to support free drug for the phase II portion of this trial. This is anticipated to greatly entice accrual for this portion of the study.

C. Changes that had a significant impact on expenditures
Due to slower then anticipated progress in completing the phase I study, the phase II has not yet started. This delay will push back completion of the research project. As such, a no-cost extension has been granted for a fourth year of research. From an expenditure standpoint, all expenditures budgeted for outside site accruals have been separated from the internal University of Chicago operating budget and will not be affected by the extension. The extension will affect salary support for the PI and study personnel as there is not a budget for these salaries for a fourth year. In the fourth year, salary support will therefore be provide through internal funds. This has been discussed with and agreed upon by the Section Chief, and senior co-Investigator on this study, Dr. Stadler. There is no expenditure changes otherwise in year 2 nor anticipated for year 3.

D. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: Nothing to report
E. Significant changes in use or care of human subjects: Nothing to report
F. Significant changes in use or care of vertebrate animals: Nothing to report

G. **Significant changes in use of biohazards and/or select agents:** Nothing to report

6. PRODUCTS:

A. Publications, conference papers, and presentations: Nothing to report

B. Website(s) or other Internet site(s): Nothing to report

C. Technologies or techniques: Nothing to report

D. Inventions, patent applications, and/or licenses: Nothing to report

E. Other Products: Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

A. What individuals have worked on the project?

Key Study Personnel	Study Roles and Responsibilities	Nearest Person Month, source of funding
Name: Russell Szmulewitz, MD Affiliated Institution: University of Chicago	Study Role(s): Principal Investigator Responsibilities: Study oversight and conduct	2, PC121149 award and University of Chicago internal funds
Name: Elia Martinez, RN, OCN Affiliated Institution: University of Chicago	Study Role(s): Research Nurse Responsibilities: Coordinates research activities for the patients on the study	2, PC121149 award and University of Chicago internal funds
Name: Jaclyn Peterson Affiliated Institution: University of Chicago	Study Role(s): Study Coordinator Responsibilities: Data manager for the study. Took over role from Jeff Bozeman mid-year.	2, PC121149 award
Name: Walter Stadler, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual, research activities and data analysis	0.5 month, University of Chicago internal funds
Name: Peter ODonnell, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual	0
Name: Chadi Nabhan, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual	0
Name: Mark Ratain Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with data acquisition and analysis	0.5 month, University of Chicago internal funds

Name: Theodore Karrison, PhD Affiliated Institution: University of Chicago	Study Role(s): Biostatistician Responsibilities: Generation of randomization algorithm and assistance with data analysis	1, PC121149 award and University of Chicago internal funds
Name: Sumati Murli, PhD Affiliated Institution: University of Chicago	Study Role(s): Independent Safety Monitor Responsibilities: Oversee study accuracy of interventions, adherence to protocol guidelines, review study recruitment and the weekly data safety monitoring minutes for the trial and coordinate/oversee review of data matching and data collection across the trial.	1, PC121149 award and University of Chicago internal funds
Name: Daniel Bennett Affiliated Institution: InVentiv Health	Study Role(s): Pharmacokinetic laboratory supervisor Responsibilities: oversight and analysis of pharmacokinetic laboratory studies (does not have access to patient identifying information)	1, Medivation Inc

B. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

C. What other organizations were involved as partners?
Inventive Health, Inc. is a central laboratory that we have contracted with that is performing the PK analyses embedded within this trial. It is a fee for service agreement with the cost of the analysis being supported through Medivation Inc (Pharmaceutical Company that manufactures enzalutamide).

1. Organization Name: InVentiv Inc.
2. Location of Organization: Princeton, NJ
3. Partner's contribution to the project
    a. Facilities: provide facilities for PK analysis
    b. Collaboration: Samples collected on the trial are sent to InVentiv, who then analyze the samples and provide a report of the enzalutamide and metabolite levels to the University of Chicago.
4. Organization Name: Medivation Inc.
5. Location of Organization: San Francisco, CA
6. Partner's contribution to the project
    a. Financial: provide financial support for PK analysis

8. SPECIAL REPORTING REQUIREMENTS
None

9. APPENDICES
None